UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/553,869 | 10/21/2005 | Rikke Hoegh Lorentsen | 66611.000013 | 1881 |

20306 7590 06/14/2010

MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

| EXAMINER | |
|---|---|
| SWOPE, SHERIDAN | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1652 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 06/14/2010 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/553,869 | LORENTSEN ET AL. | |
| | Examiner | Art Unit | |
| | SHERIDAN SWOPE | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,4,6,8-41 and 43-51* is/are pending in the application.

4a) Of the above claim(s) *12 and 18-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,6,8-11,13-17,40,41 and 43-51* is/are rejected.

7)☒ Claim(s) *1, 4, 6, 8-11,13-17, 40, 41, and 43-51* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

Based on Applicants' Appeal Brief of March 3, 2010, prosecution on this Application is REOPENED.

Claims 1, 4, 6, 8-41, and 43-51 are pending. The elected invention is directed to a method of cleaving a fusion protein using a human Granzyme B enzyme, wherein the fusion protein comprises the cleavage motif IEAD. Claims 12 and 18-39 were previously withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claims 1, 4, 6, 8-11, 13-17, 40, 41, and 43-51 and are hereby reexamined.

***Claims-Objections***

Provisional objection to Claims 1, 4, 6, 8-11, 13-17, 40, 41, and 43-51 for reciting non-elected subject matter is maintained.

Claim 1(c) is objected to for "a the".

***Claim Rejections - 35 USC § 112-Second Paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 40-45 and 47-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the following reasons.

For Claim 40, the phrase "a Granzyme B cleavage site….cleaving the fusion protein" without recitation of using a Granzyme B protease renders the claim indefinite. It is unclear whether Claim 40 means to recite using a Granzyme B protease or encompasses using any

protease. The skilled artisan would not know the metes and bounds of the recited invention. Claims 40-45 and 47-51, as dependent from Claim 40, are indefinite for the same reason. For purposes of examination, it is assumed that Claim 40 means to recite using a Granzyme B protease.

Claims 47-50 are rendered indefinite for improper antecedent usage as follows.

For Claims 47-50, "the Granzyme B protease" lacks antecedent basis.

Any subsequent rejection based, on clarification of the above phrases and terms, will not be considered a new ground for rejection.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Rejection of Claims 1, 9-11, 16, 17, 40, 44-46, 50, and 51 under 35 U.S.C. 103(a) as being unpatentable over Azad et al, 1994 in view of Harris et al, 1998 and further in view of Casciola-Rosen et al, 1999, for reasons explained in the prior action, is maintained.

In support of their request that this rejection be withdrawn, Applicants provide the following arguments. These arguments are not found to be persuasive for the reasons following each argument.

(A) The instant claims are directed to a method for the preparation of a polypeptide of interest in authentic form. This feature of the instant claims is not taught or suggested in Azad, et al., or Harris, et al., or Casciola-Rosen, et al. The failure of the references to teach or suggest

each and every feature of the instant claims is fatal to an obviousness rejection under 35 U.S.C. § 103. Section 2143.03 of the MPEP requires the "consideration" of every claim feature in an obviousness determination. To render the instant claims unpatentable, the Office must do more than merely "consider" each and every feature for this claim. Instead, the asserted references, individually or in combination, even if supported by the motivation to combine, must also teach or suggest each and every claim feature. See In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974) (to establish prima facie obviousness of a claimed invention, all the claim features must be taught or suggested by the prior art).

In a brand new case, the Federal Circuit reiterated that in order to support a conclusion of obviousness, the combined prior art must teach all of the elements of the claimed invention. Honeywell Int'l Inc. v. United States, Docket No. 2008-5181 (Fed. Cir., Feb. 18, 2010). See also In re Wada and Murphy, Appeal 2007-3733, citing In re Ochiai, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (a proper obviousness determination requires that an Examiner make "a searching comparison of the claimed invention- *including all its' limitations* -with the teaching of the prior art." (emphasis in original)). The Supreme Court has long held that obviousness is a question of law based on underlying factual inquiries, including ... ascertaining the differences between the claimed invention and the prior art. Graham v. John Deere Co., 383 U.S. 1,148 USPQ 459 (1966).

MPEP § 2143 requires that the prior art provide at least a suggestion of all of the features of a claim in the prior art. This suggestion should serve as the foundation of an "articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." KSR

Int'l v. Teleflex Inc., 127 S. Ct. 1727, 1741 (2007) (quoting In re Kahn, 441 F.3d 977, 988 (Fed. Cir. 2006).

(A) Reply: Applicants' primary argument is that all features of the recited invention, specifically, preparation of a polypeptide of interest in authentic form, are not taught by the combination of the prior art references.

The specification provides the following definition:

> 'In accordance with the present invention there is provided a method for producing polypeptides of interest in authentic form. As used herein, the term "authentic form" refers to a polypeptide which comprises the amino acid sequence thereof without any additional amino acid residues.' ...Thus, in the present context the polypeptide of interest in authentic form refers to a polypeptide having the same primary amino acid sequence as that encoded by the native gene sequence coding for the polypeptide of interest, i.e. it does not contain any non-native amino acids. The term "native gene sequence" is not necessarily a gene sequence that occurs in nature, but it may also be partly or completely artificial. Likewise it will be appreciated that a polypeptide of interest in authentic form not necessarily is a polypeptide that occurs in nature, but it may also be partially or completely artificial. (parg brdg pg 6-7; Examiner's emphasis)

The fusion proteins to be used in the methods rendered obvious by the combination of Azad et al, Harris et al, and Casciola-Rosen et al have the structures:

(i) GST-IEAD↓[N-Met-Gly-nef27-C] and (ii) $HIS_{6X}$-IEAD↓[N-Met-Gly-nef27-C]

wherein GST and $HIS_{6X}$ are fusion partners, -[N-Met-Gly-nef27-C] is the authentic sequence for nef27, IEAD is the elected cleavage motif for Granzyme B, and ↓ indicates the cleavage position for Granzyme B. In the method rendered obvious by the combination of Azad et al, Harris et al, and Casciola-Rosen et al, cleavage of the either of the fusion proteins by human, mouse, or rat Granzyme B, produces authentic nef27. Moreover, the penultimate amino acid at the N-terminus of nef27 is glycine, as recited in Claim 4. Thus, all features of Claims 1, 9-11, 16, 17, 40, 44-46, 50, and 51 are taught by the combination of the prior art references.

KSR International vs Teleflex Inc. (Federal Register/ Vol. 72, No. 1995, October 10,

2007) takes precedent in the Office's current determination of obviousness under §103(a).

Therein, rationales supporting an obviousness rejection are (72 Fed. Reg. 57526; esp pg 57529):

(a) combining prior art elements according to known methods to yield predictable results,
(b) simple substitution of one known element for another to obtain predictable results,
(c) use of a known technique to improve similar devices (methods or products) in the same way,
(d) applying a known method to a known product or method ready for improvement to yield a predictable result,
(e) "obvious to try" –choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success,
(f) known work in one filed of endeavor may prompt variations for use in the same or a different field, if the variants would have been predictable, and
(g) some teaching, suggestion, or motivation in the prior art to lead the skilled artisan to modify or combine prior art teachings.

In the instant case, the relevant rationales for supporting the obviousness rejection are (a) combining the prior art references will, more likely than not, lead to the predicated result of a method of producing authentic nef27 by cleaving the fusion protein (i) GST-IEAD↓[N-Met-Gly-nef27-C] or (ii) $HIS_{6X}$-IEAD↓[N-Met-Gly-nef27-C] with Granzyme B, (b) simple substitution of one known element for another to obtain the above described predictable result, (c) use of a known technique to improve the method of Azad et al by incorporating the teachings of Harris et al and Casciola-Rosen et al, and (g) as explained in the prior action, based on knowledge of the skilled artisan, there would be motivation to combine the teachings of Azad et al, 1994 in view of Harris et al, 1998 and further in view of Casciola-Rosen et al, 1999 to produce authentic nef27.

(B) Regarding Harris et al, Figure 5 and the remainder of Harris et al teaches the cleavage of a fusion protein to produce a pIII coat protein of M13 bacteriophage. Harris et al discloses a six amino acid motif, IEADSAL, that is explained as essential for Granzyme B cleavage (Abstract and Figure 5). The amino acids following the cleavage site, the P 1' and P2' amino

acids and a linker (AGPGGG), are not part of the authentic polypeptide sequence of the pIII coat protein of M 13 bacteriophage (p. 27365, last paragraph of col. 2). Therefore, following cleavage at the cleavage site (↓), the polypeptide of interest is left with two non- authentic peptides (AL) at the N-terminus.

Harris et al provides no reason for one of ordinary skill in the art to use its method to produce a polypeptide in authentic form as presently being claimed. Indeed, Harris, et al. teaches away from the present invention because Harris, et al. teaches the necessity of P1' and P2' amino acids (amino acids that are in the C-terminal direction from the cleavage site).

Furthermore, instead of teaching or suggesting the production of a polypeptide of interest in authentic form, Harris, et al. describes the cleavage of a variety of short synthetic amide substrates produced via a combinatorial library as shown in Tables 2 and 3. Harris, et al. merely identifies a handful of six amino acid sequences and the specific site of Granzyme B cleavage and provides no mention or suggestion to use Granzyme B for the purification of a protein of interest in authentic form. To put it another way using the words of the CAFC in In re O' Farrell, Harris et al. gives one skilled in the art "no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful" to arrive at the claimed invention. In re O'Farrell, 853 F.2d 894, 895 (Fed. Cir. 1988).

(B) Reply: The fact that Harris et al teaches production of a pIII coat protein of M13 bacteriophage is irrelevant to the instant invention. As explained in the Action of April 7, 2009, the relevant teachings of Harris et al are that Granzyme B cleaves at the motif IEAD↓Xaa-Gly, wherein Xaa can be any amino acid (Abstract; Fig 5). It is noted that "IEAD" is the Granzyme B cleavage motif elected by Applicants in their telephonic response of November 13, 2007.

Harris et al does not teach the necessity of any specific residue in the P1' position (Abstract; Fig 5). The P2' glycine taught by Harris et al is represented by the penultimate residue in authentic nef27, as taught by Azad et al (pg 651, parg 2; encoded by ATG-GGT).

Harris et al clearly teaches motifs that can be cleaved by Granzyme B, which is relevant to the instant rejection. As explained above, (A), KSR International vs Teleflex Inc. (Federal Register/ Vol. 72, No. 1995, October 10, 2007) takes precedent in the Office's current determination of obviousness under §103(a).

(C) Azad, et al. does not teach the production of a polypeptide of interest in authentic form.

The examiner refers to p. 651, ¶ 2 of Azad for a teaching that a nef27 polypeptide contains Met-Gly at the N-terminus. See Office Action mailed April 7, 2009, p. 6 and Advisory Action. However, Azad, et al. teaches the production of the nef27 protein using the pGEX-2T fusion vector described in Azad, et al (p. 651, last paragraph). This vector includes a thrombin recognition sequence and cleavage site in the GST peptide encoded by the vector: Leu-Val-Pro-Arg↓Gly-Ser, wherein "↓" is the thrombin cleavage site (Ex. A (Evidence Appendix) which is a map of the pGEX-2T vector showing the cleavage site). Therefore, the Nef protein derived from thrombin-cleaved GST-Nef (see p. 653) is left with Gly-Ser from the vector at the N-terminus. Because the Nef peptide produced as described in Azad, et al. has non-native amino acids left over from the vector (Gly-Ser) at the N- terminus, Azad, et al. does not teach the production of a polypeptide in authentic form as presently claimed.

(C) Reply: It is acknowledged that Azad et al does not teach the production of a polypeptide of interest in authentic form. As explained in the prior actions and above, it is the

combination of Azad et al, Harris et al, and Casciola-Rosen et al that teaches the production of a polypeptide of interest in authentic form.

As explained in the prior actions, the method rendered obvious by the combination of Azad et al, Harris et al, and Casciola-Rosen et al uses Granzyme B and the motif "IEAD" to prepare authentic nef27. The relevant teaching of Azad et al is the generic idea of cleaving a fusion protein comprising nef27 to release a nef27 protein. The teachings of Azad et al regarding the Leu-Val-Pro-Arg↓Gly-Ser motif and cleavage with thrombin are not used for the instant rejection.

(D) Casciola-Rosen et al teaches a number of Granzyme B cleavage motifs, but it does not teach cleavage of fusion proteins or the production of a polypeptide in authentic form.

Moreover, while Casciola-Rosen, et al. teaches a number of Granzyme B cleavage motifs, it does not teach cleavage of fusion proteins or the production of a polypeptide in authentic form. Thus, Casciola-Rosen, et al. does not cure the deficiencies of Harris, et al. and Azad, et al.

(D) Reply: It is acknowledged that Casciola-Rosen et al does not teach cleavage of fusion proteins or the production of a polypeptide in authentic form. As explained above and in the prior action, it is Azad et al that teaches the generic idea of cleaving a fusion protein to release a protein therein. As explained above and in the prior action, the relevant teaching of Casciola-Rosen et al is that Granzyme B was known in the art. As explained above and in the prior action, it is the combination of Azad et al, Harris et al, and Casciola-Rosen et al that teaches the production of a polypeptide in authentic form.

(E) The claimed invention provides unexpected results. Compared to methods of preparing fusion proteins with other proteases known in the art, Granzyme B protease provides significant and unexpected improvement over the existing cited art. Granzyme B is (a) more specific than other proteases and avoids cleavages in the middle of the protein of interest, (b) permits the purification of authentic forms of proteins of interest with no extraneous amino acids at the amino terminus thereby improving native confirmation, and (c) provides a more efficient cleavage than other proteases, which reduces production costs by reducing wasted uncleaved fusion protein (specification, pp. 3-5, and 62). Nothing in the cited art suggests to the skilled artisan that these goals can be accomplished using a Granzyme B protease as claimed.

In light of the arguments presented above, Applicants respectfully submit that Azad, et al. in view of Harris, et al., and further in view of Casciola-Rosen, et al. do not render obvious independent claims 1 and 40, and dependent claims 9-11, 16, 17, 44-46, 50, and 51. Accordingly, Applicants respectfully request that the rejection of these claims under 35 USC § 103(a) be reversed.

(E) Reply: Applicants' arguments for unexpected results is not persuasive for the following reasons. (a) Applicants' assertion that Granzyme B is more specific than other proteases does not provide unexpected results since Granzyme B and it's cleavage specificity was known in the art. (b) Based on the combination of Azad et al, Harris et al, and Casciola-Rosen et al, the fact that Granzyme B permits the purification of authentic forms of proteins of interest with no extraneous amino acids at the amino terminus thereby improving native confirmation is not unexpected. (c) It is acknowledged that the specification at pages 3-6 describe a problem in the art, the inefficiency of fusion protein cleavage, while page 62 describes

the efficiency of linking Granzyme B to a solid support. None of pages 3-6 or 62 describe Granzyme B as being a more efficient protease than any other protease. Moreover, if Granzyme B is a more efficient protease, which the specification does not demonstrate on pages 3-6 or 62, said higher efficiency is inherent to the method rendered obvious by the combination of Azad et al, Harris et al, and Casciola-Rosen et al.

For these reasons and those explained in the prior actions, rejection of Claims 1, 9-11, 16, 17, 40, 44-46, 50, and 51 under 35 U.S.C. 103(a) as being unpatentable over Azad et al, 1994 in view of Harris et al, 1998 and further in view of Casciola-Rosen et al, 1999, is maintained.

Rejection of Claims 4, 6, and 41 under 35 U.S.C. 103(a) as being unpatentable over the combination of Azad et al, 1994, Harris et al, 1998, and Casciola-Rosen et al, 1999 in view of Boutin et al, 1997, for reasons explained in the prior action, is maintained. In support of their request that said rejection be withdrawn, Applicants provide the following arguments. These arguments are not found to be persuasive for the reasons following each argument.

(A) For the reasons described above, claims 1, 9-11, 16, 17, 40, 44-46, 50, and 51 are not obvious over Azad, et al., Harris, et al., and Casciola-Rosen, et al.

(A) Reply: This argument is not found persuasive for the reasons explained above.

(B) Boutin, et al. does not add to the case of obviousness against claims 1, 9- 11, 16, 17, 40, 44-46, 50, and 51. Applicants understand that the Examiner has added Boutin, et al. to the above-discussed rejection over Harris, et al., Azad, et al., and Casciola-Rosen, et al. in order to specifically address claims 4-6, and 41, which are directed to the use of the claimed method wherein the penultimate amino acid adjacent the cleavage site is glycine (claim 4), and polypeptide of interest is an enzyme (claims 5-6 and 41).

(B) Reply: It is acknowledged that Boutin et al is not needed for rejection of Claims 1, 9-11, 16, 17, 40, 44-46, 50, and 51 under 35 U.S.C. 103(a) as being unpatentable over Azad et al, 1994 in view of Harris et al, 1998 and further in view of Casciola-Rosen et al, 1999. Boutin et al was used because, as explained in the prior action, the combination of Azad et al, Harris et al, and Casciola-Rosen et al fails to teach production of an authentic enzyme, as recited in Claims 4, 6, and 41. Nonetheless, it is noted that the subject matter of Claims 4, 6, and 41 is encompassed by one or more of Claims 1, 9-11, 16, 17, 40, 44-46, 50, and 51.

(C) The Examiner's reasoning regarding the myristoylation of polypeptides and the removal of the N-terminal methionine are not relevant to the obviousness rejection. Even assuming that the Met was present, or that the protein is myristolyated, the Examiner's only reasoning for using Boutin, et al. in the rejection is that one of skill in the art would be motivated to produce Calcineurin B. See Office Action mailed April 7, 2009, p. 8. Apparently, the only reason that Boutin, et al. is used in the rejection is related to the fact that Calcineurin is an enzyme that, assuming the Met is counted, would have a glycine that is penultimate to the N-terminus.

(C) Reply: It is acknowledged that Boutin, et al, in view of the combination of Azad et al, Harris et al, and Casciola-Rosen et al, renders obvious a method for making an authentic enzyme having a glycine that is penultimate to the N-terminus.

(D) These reasons do not add to the case of obviousness based upon Harris, et al., Azad, et al., and Casciola-Rosen, et al., alone, including with regard to dependent claims 4-6 and 41. With regard to independent claims 1 and 40, Boutin, et al. is not cited as teaching fusion proteins, any proteases cleaving fusion proteins, or the production of polypeptides using fusion

proteins or proteases. Therefore, Boutin, et al. is irrelevant to claims 1 and 40. Therefore, the sole fact that Calcineurin B is an enzyme would not motivate one of skill in the art combine Boutin, et al. with Harris, et al., Azad, et al., or Casciola-Rosen, et al.

(D) Reply: It is acknowledged that Boutin et al does not teach fusion proteins, any proteases cleaving fusion proteins, or the production of polypeptides using fusion proteins or proteases. It is the combination of Azad et al, Harris et al, and Casciola-Rosen et al that teaches fusion proteins, any proteases cleaving fusion proteins, or the production of polypeptides using fusion proteins and proteases, as encompassed by the claims. Nonetheless, Boutin et al is relevant to Claims 1 and 40 because said claims encompass the subject matter of Claims 6 and 41, which recite production of an authentic enzyme.

Rejection of Claims 13-17 and 47-49 under 35 U.S.C. 103(a) as being unpatentable over the combination of Azad et al, 1994, Harris et al, 1998, and Casciola-Rosen et al, 1999 in view of Sigma Inc, 1998 or Pharmacia, Inc, for reasons described in the prior action, is maintained.

In support of their request that said rejection be withdrawn, Applicants provide the following argument. Sigma Inc. 1998 and Pharmacia, Inc. do not cure the deficiency of the combination of Azad, et al., Harris, et al., and Casciola-Rosen, et al. to render obvious claims 1, 9-11, 16, 17, 40, 44-46, 50, and 51, which includes independent claims 1 and 40, as discussed above. Applicants understand that this rejection is directed specifically to claims 13-15 and 47-49, which are directed to embodiments of the invention wherein the Granzyme B protease is in an immobilized form.

This argument is not found to be persuasive for the following reason. The teachings of Sigma Inc. 1998 and Pharmacia, Inc are relevant to Claims 1 and 40 because said claims

encompass the subject matter of Claims 13-15 and 47-49, which recite use of immobilized Granzyme B.

Claims 8 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wan et al, 1996 in view of Bleackley et al, 1988 and further in view of Harris et al, 1998. Wan et al teaches a method for production of authentic HIV-1 protease, wherein the method uses fusion proteins comprising HIV-1 protease that proteolytically autoprocesses, thereby producing the active authentic HIV-1 protease (pg 572, parg 2; Fig 3). Wan et al does not teach a method for production of authentic Granzyme B protease, wherein the method uses fusion proteins comprising Granzyme B protease that proteolytically autoprocesses, thereby producing the active authentic Granzyme B protease. Bleackley et al teaches that Granzyme B is synthesized as a prepro-form, which must be processed to remove the first 20 amino acids for activation (pg 155, parg 4). Bleackley et al further teaches that the site of said processing occurs within the motif GAEE↓II (Fig 1). It would have been obvious to a person of ordinary skill in the art to adapt the method of Wan et al to make a method for production of authentic Granzyme B protease, wherein the method uses fusion proteins comprising Granzyme B protease that proteolytically autoprocess. In said adapted method, the motif GAEE↓$II^2$ in Granzyme B would be replaced with the motif IEAD↓$IG^2$ which, as taught by Harris et al, is a motif cleaved by Granzyme B (Fig 5). The resulting fusion protein would consist of an N-terminal fusion partner linked to the prepro region of Granzyme B, or a fragment thereof, followed by the IEAD↓$IG^2$ Granzyme B cleavage motif, wherein $IG^2$ begins the sequence for the authentic active region of Granzyme B. Said fusion protein would proteolytically autoprocess, thereby producing the active authentic Granzyme B protease. Motivation to make such a method is provided by the desire to produce

the active Granzyme B protease and to screen for inhibitors of auto-processing. The expectation of success is high, as the making and autoprocessing of fusion proteins was known in the art. In addition, the skilled artisan would believe that, more likely than not, the $Ile^2Gly$ substitution at the penultimate position of Granzyme B would not affect Granzyme B protease activity. Therefore, Claims 8 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wan et al, 1996 in view of Bleackley et al, 1988 and further in view of Harris et al, 1998.

Regarding the above rejection, it is noted that the specification provides the following definition:

> 'In accordance with the present invention there is provided a method for producing polypeptides of interest in authentic form. As used herein, the term "authentic form" refers to a polypeptide which comprises the amino acid sequence thereof without any additional amino acid residues.' ...Thus, in the present context the polypeptide of interest in authentic form refers to a polypeptide having the same primary amino acid sequence as that encoded by the native gene sequence coding for the polypeptide of interest, i.e. it does not contain any non-native amino acids. The term "native gene sequence" is not necessarily a gene sequence that occurs in nature, but it may also be partly or completely artificial. Likewise it will be appreciated that a polypeptide of interest in authentic form not necessarily is a polypeptide that occurs in nature, but it may also be partially or completely artificial. (parg brdg pg 6-7; Examiner's emphasis)

***Allowable Subject Matter***

No claims are allowable.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Regarding filing an Appeal, Applicants are referred to the Official Gazette Notice published July 12, 2005 describing the Pre-Appeal Brief Review Program.

**Final Comments**

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SHERIDAN SWOPE/
Primary Examiner, Art Unit 1652

/Andrew Wang/
Supervisory Patent Examiner, Art Unit 1652